Journal of Molecular Structure 1167 (2018) 69–77

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Spatial structure of atorvastatin and its complex with model membrane in solution studied by NMR and theoretical calculations

L.F. Galiullina*, G.S. Musabirova, I.A. Latfullin, A.V. Aganov, V.V. Klochkov

Kazan (Volga Region) Federal University, 18 Kremlevskaya St., 420008, Kazan, Russian Federation

ARTICLE INFO

Article history:
Received 29 December 2017
Received in revised form
6 March 2018
Accepted 2 April 2018
Available online 27 April 2018

Keywords:
Atorvastatin
Statins
NMR
Nuclear overhauser effect
Dodecylphosphocholine micelles
Molecular complex

ABSTRACT

Atorvastatin is a drug of the statin group which possesses the ability to decrease low-density lipoprotein cholesterol level by the competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. There is a hypothesis that pharmacological properties of statins depend on their location in the cell membrane. Intermolecular complex of atorvastatin with dodecylphosphocholine (DPC) micelle was investigated by NMR and computational methods. The results of NMR experiments showed that atorvastatin forms molecular complex with model membrane in solution by penetrating a space between hydrocarbon chains of the DPC micelle. Analysis of obtained data in comparison with previously reported results for simvastatin, pravastatin, fluvastatin and cerivastatin showed that locations of statins in model membranes correlate with their pharmacological features, such as efficacy and risk of rhabdomyolysis.

1. Introduction

Atorvastatin is a drug of the statin group which possesses the ability to decrease low-density lipoprotein (LDL) cholesterol level by the competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. It is a calcium salt containing a fragment of β,δ-dihydroxy-heptanoic acid, an analogue of mevalonate [1,2]. Even though all statins share common pharmacophore group essential for inhibition of cholesterol biosynthesis their pleiotropic features are quite different [3–7]. Different trials and clinical findings support the hypothesis that there are important intermolecular differences responsible for broader pharmacologic actions of statins, even beyond HMG-CoA reductase inhibition [8,9]. Nevertheless, by now there is no definitive explanation for the origin of differences in efficiency, safety, and potential non-LDL actions of statins. There is a hypothesis that pharmacological properties of statins depend on their location in the cell membrane [10–13]. There is a lack of studies on statins interactions with the surface of the cell membrane in solid state, and there is almost no such information about interactions in liquid media presented in literature. However, this information is necessary for understanding of physiological actions of the drugs because solution is a native environment for the processes in human organism.

One of the most effective methods for investigation of molecular structure of different medicines in liquids is nuclear magnetic resonance spectroscopy [14–17]. It is allowing determination of molecular spatial structure and the structure of molecular complexes using the most effective for such purposes technique NOESY, which is based on a measurement of nuclear Overhauser effect (NOE). Unfortunately, there are difficulties in studying interactions of drugs with cell surface in solution directly by NMR due to very short T_2 proton relaxation times of phospholipid membranes leading to extensive broadening of NMR signals [18,19]. Even so, complexation of different pharmaceuticals with cell membranes can be effectively studied by NMR using model systems such as dodecylphosphocholine (DPC) micelles, which are widely used for imitation of cell membrane in the NMR experiments [20–23]. DPC molecule contains the same head group as phosphatidylcholines and, therefore, effectively mimics eukaryotic membrane. Our group previously has shown that pravastatin, simvastatin, fluvastatin and cerivastatin form intermolecular complexes with model membranes, and the structures of the complexes are different [13,24–26]. It was suggested that distinctions in locations of statins

* Corresponding author.
E-mail address: lgaliull@kpfu.ru (L.F. Galiullina).

https://doi.org/10.1016/j.molstruc.2018.04.012
0022-2860/